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FORMULATION AND EVALUATION OF ASCORBIC ACID EXTENDED RELEASE HYDROPHYLLIC MATRIX TABLETS BY USING HYDROXYPROPYL METHYL-CELLULOSE AND POLYETHYLENE OXIDE AS MATRIX FORMING POLYMERS

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Summary

Aim: Developing extended release matrix tablets containing 350 mg ascorbic acid and hydroxypropyl methylcellulose (HPMC) or polyethylene oxide (PEO) as hydrophilic polymer/s which control the rate and degree of drug release through 12 hour period.
Materials and methods: Six batches of matrix tablets (P1, P2, P3, P4, P5, P6) were produced by direct compression. Ascorbic acid 97% was used as active compound. HPMC K4M, HPMC K15M, PEO 1105 and PEO 301 were used as hydrophilic polymers. Cellulose microcrystaline was used as diluent, copovidone was employed as binder, colloidal silica as flow-aid while magnesium stearate was used as lubricant. Before tableting powder mixtures were sieved and evaluated for bulk density, tapped density, angle of repose, compressibility index and Hausner ratio. Compressed tablets were evaluated for average mass, hardness, friability, average drug content and dissolution profile through 12 hours in phosphate buffer pH=7.2 . All test were conducted according pharmacopoeial standards (PhEur 7 and USP 35)
Results: All six batches of powder mixtures demonstrated good flow properties and didn't tend to make any problems during tableting process. Also all six batches of tablets complied the pharmacopeial requirements concerning average mass, hardness, friability and drug content. Dissolution studies demonstrated that all six batches of tablets provided extended release of ascorbic acid through 12 hours period, but only tablets containing PEO 1105, PEO 301 and their 1:1 mixture liberated more than 80% active compound, which is generally due to the lower viscosity and higher erodability of these PEO-s compared with the used HPMC-s. It was also demonstrated that low viscosity PEO 1105 or HPMC K4M released higher percent of active compound compared with higher viscosity PEO 301 or HPMC K15M, while both PEO 1105/PEO 301 1:1 mixture and HPMC K4M/HPMC K15M 1:1 mixture gave intermediate drug release, which is connected to the intermediate viscosity obtained by mixing these polymers.
Conclusion: From the results received from all test it was concluded that tablets containing PEO 1105 as hydrophilic polymer (P1) are the most suitable choice for developing 12 hour extended release matrix tablets containing 350mg ascorbic acid as active compound.

Key words: ascorbic acid, extended release tablets, polymer, hydroxypropyl methylcellulose, polyethylene oxide

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Introduction

Ascorbic acid (Vitamin C) is a hydrosoluble essential vitamin. Because of the incapability to be produced by the body, humans must supply vitamin C via food (especially fruits and vegetables) and/or via health supplements. Ascorbic acid is best known by its antioxidant activity, and the free radical scavenging [Heber,2007]. Thereby it is very important for tissue recovery, collagen synthesis, and many oxidation-reduction reactions in the organism. Ascorbic acid also takes part in the metabolism of folic acid, tyrosine, phenylalanine, iron, histamine etc. It supports the immune system, it protects blood vessels, it increases the absorption of iron in the GUT. Deficiency of ascorbic acid in the human body may cause scurvy, anemia, atherosclerotic plaques, bleeding gums, muscle degeneration, neurotic disturbances, poor wound healing [Iqbal et al, 2004]. The required daily dose of ascorbic acid varies among the nutritional scientist from several mg up to 1-2 g. The absorption of the vitamin C from the GUT is up to70% when smaller amounts are ingested (up to 180 mg). By increasing the dose the % of absorbed vitamin C decreases down to 50% - 15% [Iqbal et al,2004] Many countries have estimated 60 mg ascorbic acid as RDA and 350 mg ascorbic acid as MDA for a dietary/health supplement [Official gazzete of R.Macedonia]. Developing extended release dosage form of ascorbic acid will provide continuous supply of small amounts of the active moiety which could be easily absorbed from the human GUT.

Extended release drug formulations became very popular in the last two decades, since they overcame some of the disadvantages of conventional solid dosage forms (tablets and capsules) such as fluctuations of the drug concentration in the plasma and on the site of action, frequency of dosing, drug toxicity, costs etc [Aulton, 2007].After administration extended release dosage forms provide continuous supply of small but therapeutic amounts of active compound at rates sufficiently controlled to provide maintaining therapeutic plasma concentration levels and prolonged therapeutic action (usually between 8-12 hours). The main goal of formulators working on extended release dosage forms in to achieve linear zero order release of the active moiety. There are several types of dosage forms which provide extended release of the active compound, and could be designed as mono- or multi-dose units. Those are:

-Matrix systems (hydrophilic and hydrophobic)

-Membrane controlled systems

-Osmotic systems

Hydrophilic matrix systems/tablets or also called swellable-soluble systems are the most investigated type of extended release dosage forms. They consist of mixture of active compound and a hydrophilic polymer, usually with added suitable diluent/s, binders, lubricants etc. These types of dosage forms may be produced by both direct compression or granulation methods [Wen et al, 2010].Hydrophilic matrix tablets, achieve extended release of an active compound in presence of water by rapid hydration and swelling of the polymer located on the outer surface of the tablet and formation of an outer porous gelatinous layer [Wen et al, 2010].This layer maintains tablet integrity and prevents rapid disintegration. It also controls the diffusion of the water medium inside the matrix, and this is the reason why the outer gel layer plays important role in controlling the rate of drug release. Fast formation of an outer gelatinous layer is crucial for obtaining suitable extended release matrix tablet.

Hydrophilic matrix tablets release the active compound via two main mechanisms: diffusion and erosion. By hydration and swelling the polymer content on the outer surface of the tablet forms a continuous porous gel layer which enables water to penetrate inside the hydrated and swelled part of the matrix and to dissolve the active compound. The dissolved substance leaves the matrix by diffusion through the gel layer. When the outer gel layer fully hydrates it starts to erode and it is continuously replaced by new hydrated polymeric

layer. By erosion of the matrix surface an amount of active compound is released in the outer media [Wen et al, 2010]. Therefore it could be concluded that the release of the drug from a hydrophilic matrix system depends mainly on polymer features such as: molecular weight, viscosity and swelling capacity, permeability and erosion of the outer gel layer but also it is connected with properties such as: drug solubility and matrix composition. [Salah et al, 2010] The higher the molecular weight and viscosity of the polymer are, longer time period is required for complete drug release. Usually hydrophilic matrix systems/tablets release the active compound by both diffusion and erosion.

Hydroxypropyl methylcellulose (HPMC, Hypromelose) or METHOCEL™ (marketed by Dow and Colorcon) is most widely used hydrophilic water soluble polymer for preparation of hydrophilic matrix systems/tablets. It is compatible with many active compounds and with most of the excipients used in modern solid dosage forms, it is pH independent, it has good flowability and compressibility, and gives tablets with reproducible characteristics. HPMC appear in different molecular weights and with different viscosity grades, which makes it suitable for many pharmaceutical purposes (modified release, tablet coating, tablet binding etc)[Rowe et al, 2006]. High viscosity grade HPMC-s (Methocel K4M, Methocel K15M, Methocel K100M) are mostly used as a modified release polymers. They show quick hydration and formation of a continuous gel layer which provide controlled release of the active compound by both diffusion and erosion while maintaining tablet integrity during prolonged time periods [Tu et al, 2010].An effort to formulate 100 mg ciprofloxacine hydrochloride with HPMC K100 LV , HPMC K4M ,HPMC K15M and HPMC K100M was made by Rahman et al. The dissolution studies through 8 hours period showed that matrices containing HPMC K100 LV and HPMC K4M released more than 90 % of the active compound in 6 hours while matrices containing HPMC K15M and HPMC K100M provided extended release through 8 hours (around 90% drug released).[Rahman et al, 2011]. These results demonstrated that drug release from HPMC matrix tablets depends mainly on polymer viscosity and molecular weight.

Polyethylene oxide-s (PEO) are water soluble resins commercially known as POLYOX™ (marketed by Dow and Colorcon) which in recent years has attracted great attention as a polymeric excipient that can be used in formulation of pH independent hydrophilic matrices. Due to their chemical structure, PEO-s are among various hydrophilic polymers that, in the presence of water, supply the active moiety in controlled fashion by swelling and forming a hydrogel, which lead to drug release by diffusion and/or erosion [Pinto et al, 2004]. All the attention paid to PEO-s is a consequence of their physical and chemical stability, compressibility, high swelling ability, and fast hydration. Thus, PEO-s have been proposed as alternatives to HPMC or other hydrophilic polymers in the production of extended release matrix tablets. PEO-s appear in different molecular weights and viscosity grades, from which the ones with high molecular weights and high viscosity values(POLYOX 1105, POLYOX 301, POLYOX 303) are the most suitable candidates for developing hydrophilic matrix tablets [Rowe et al, 2006].. Maggi at al. investigated the dissolution profile of diltiazeme hydrochloride from matrices containing PEO 1105 and matrices containing PEO 301 made under stamp pressure of 10 kN and 30 kN [Maggi et al, 2002]. The obtained results showed that lower viscosity polymer PEO 1105 released approximately 100% active drug in period of 6 hours while matrices containing higher viscosity PEO 301 released around 75% of the incorporated diltiazem in the same time interval. The tablet hardness didn't affect the release of the active moiety in matrices containing the same polymer.

Mixing polymers from the same chemical entity but with different physical properties in different ratios provides modification of physical and chemical features of the matrix and

often leads to modification of the rate and extent of drug release [Wen et al, 2010]. This phenomenon is usually used for achieving specific release profile and site-specific activity of some active compounds.Kumar et al. studied gastro-retentive hydrophilic matrices of famotidine containing HPMC K4M and HPMC K15M, and a mixture of these two polymers in a 1:1 ratio [Kumar et al, 2009]. The obtained results showed that the formulation containing polymer blend decreased the % of drug released compared with formulations containing single polymer.

The aim of this work was to formulate hydrophilic matrix tablets containing 350 mg ascorbic acid as a model- active compound, by using two types of polymers HPMC-METHOCEL (subtypes K4M, K15M and their mixture in ratio 1:1) and PEO-POLYOX (subtypes 1105, 301 and their mixture in ratio 1:1), to compare the obtained products on the basis of physical features and drug release, and to conclude how different polymers affect the physic-chemical properties of hydrophilic extended release matrix systems.

Materials and methods

Materials

Ascorbic acid 97% DC was purchased from ALAND NUTRECEUTICAL CO. LTD. PEO-s (POLYOX 1105 and POLYOX 301) and HPMC-s (METHOCEL K4M and METHOCEL K15M) were obtained from COLORCON®, UK. Cellulose Microcrystaline (MCC) (VIVAPUR 102) was purchased from JRS PHARMA®, Germany, copovidone (Kollidon VA64) from BASF®, Germany, anhydrous colloidal silica (AEROSIL) from EVONIK®, Germany and magnesium stearate from DR.PAUL LOHMANN®, Germany.

Methods

Powder mixture treatment and evaluation

All powder compounds (except magnesium stearate) were accurately weighted, passed through standard 1.1mm sieve and thoroughly blended for 5 minutes in a PE bag. After being mixed powders were evaluated for bulk density and tapped density (PhEur 7), compressibility index (Carr's index), Housner ratio and angle of repose(standard funnel and petri dish with radius of 4.75cm).

Tablet formulation and preparation

After mixing powder compounds, Mg stearate was added to the powder mixture by passing it through a standard sieve 1.1mm. The obtained mixture was thoroughly mixed for period of 1 minute in a PE bag. Matrix tablets were prepared by direct compression using FETTE 1200 rotary tablet press. Six batches (P1, P2, P3, P4, P5, P6) of round white-yellowish tablets with average mass of 650 mg and diameter of 12 mm were obtained. Complete composition (mg) of the tablets and the role of each excipient is shown in table 1.

Table 1- Composition of P1, P2, P3, P4, P5, P6 batch of tablets and compound function

	P1	P2	P3	P4	P5	P6	function
Ascorbic acid 97%	361	361	361	361	361	361	Active compound
PEO-POLYOX 1105	195	/	97.5	/	/	/	Hydrophilic polymer/resin
PEO-POLYOX 301	/	195	97.5	/	/	/	Hydrophilic polymer/resin
HPMC-METHOCEL K4M	/	/	/	195	/	97.5	Hydrophilic polymer
HPMC-METHOCEL K15M	/	/	/	/	195	97.5	Hydrophilic polymer
Cellulose microcrystaline	64.75	64.75	64.75	64.75	64.75	64.75	Insoluble filler
Copovidone	19.5	19.5	19.5	19.5	19.5	19.5	Binder
Colloidal silica	3.25	3.25	3.25	3.25	3.25	3.25	Flow aid
Mg stearate	6.5	6.5	6.5	6.5	6.5	6.5	Lubricant
Σ	650	650	650	650	650	650	

Table 2- Average viscosity of some hydrophilic polymers

	Viscosity(mPa-s) in 1% aqueous solution	Viscosity(mPa-s) in 2% aqueous solution	Viscosity(mPa-s) in 5% aqueous solution
PEO-POLYOX 1105	/	/	8800-17600
PEO-POLYOX 301	1650-5500	/	/
HPMC-METHOCEL K4M	/	3000-5600	/
HPMC-METHOCEL K15M	/	11250-21000	/

Standard tablet evaluation

Tablets were examined on the basis of weight uniformity (Mettler Toledo balance), friability (Varian dual roche type drums), resistance to crushing (Varian VK 200), estimation of drug content (HPLC-Agilent technology 1200 RRLC, VWD detector).
Dissolution test was made in accordance with USP (paddle apparatus Varian VK7025), 75rpm speed, at temperature of 37°C, in phosphate buffer pH= 7.2 at time interval from 2,4,6,8, 10 and 12 hours . Amount of drug release was measured in the intervals of 2, 4, 6, 8, 10 and 12 hours and determined by HPLC (Agilent technology 1200 RRLC, VWD detector). Our requirement was minimal 80 % drug release in 12 hours period.
All tests were made in accordance with the current edition of the European Pharmacopeia (PhEur 7) and the United States Pharmacopeia (USP 35)

Results and discussion

Powder properties
Formulations containing HPMC had bulk density in range of 0.526 g/ml up to 0,540 g/ml and tapped density from 0.702 g/l up to 0.741 g/ml, while formulations containing PEO showed bulk density values from 0.541 g/ml up to 0.588 g/ml and tapped density values ranging from 0.678 g/ml up to 0.690 g/ml. By comparing the results obtained for Compressibility (Carr's) index, Hausner ratio and angle of repose it could be concluded that powder mixtures containing PEO (P4, P5, P6) show better flow properties compared with powder mixtures containing HPMC (P1, P2, P3). It is considered that powders having Carr's index value up to 30%, Hausner ratio value less than 1.20 and angle of repose smaller than 35° show good flow properties, and very often do not require addition of flow aid compounds [Zheng J, 2009]. However inclusion of colloidal anhydrous silica in all six formulations provided obtaining powder mixtures with good flowability, which was observed on sieving and on tableting processes [Rowe et al, 2006]. The physical properties of the powder blends are shown in Table 3.

Table 3- Physical characteristics of powder mixtures

	P1	P2	P3	P4	P5	P6
Bulk density (g/ml)	0,531	0,54	0,526	0,541	0,588	0,548
Tapped density (g/ml)	0,702	0,741	0,714	0,69	0,678	0,678
Carr's index (%)	24,36	27,12	26,33	21,59	13,27	19,17
Hausner ratio	1,32	1,37	1,36	1,27	1,15	1,24
Angle of repose	31,15	32,47	32,43	29,71	28,86	29,63

Tablet properties

By employing direct compression method on a rotary tablet press, six batches of shine white-yellowish tablets were produced. All six batches complied the pharmacopoeial requirements (PhEur 7, USP 35) concerning average mass, hardness, friability and drug content. The tableting process was continuous and provided obtaining tablets whose mass didn't tend to vary more of 1%. Tablets containing PEO showed slightly bigger hardness compared

with tablets containing HPMC. It could be also noted that tablets containing polymer with higher molecular weight(HPMC K15M, PEO 301) show higher hardness values compared to tablets composed of polymer with lower molecular weight(HPMC K4M, PEO 1105). The batches containing polymer blends tend to settle their hardness values between those shown by tablets composed of single polymers. This could be due to phenomenon of obtaining median molecular weight when mixing different polymers. It is very important to mention that all six batches of tablets had 0% mass loss after friability testing, which shows that they could withstand mechanical shock and are suitable for coating without the possibility to be physically damaged. The complete results for standard tablet properties are shown in table 4.

Table 4- Standard tablet characteristics

	P1	**P2**	**P3**	**P4**	**P5**	**P6**
Average mass (mg)	649,6	652,5	653,09	647,95	648,41	650,3
Hardness (kP)	10,42	10,93	10,56	10,81	11,04	11,51
Friability (%)	0	0	0	0	0	0
Drug content (%)	99,41	100,4	101,65	98,27	99,85	101,67

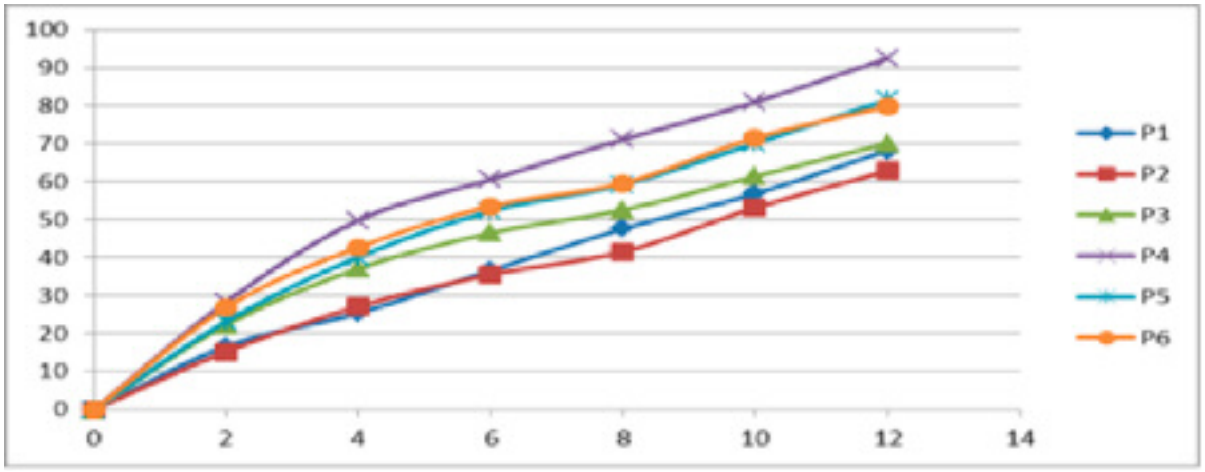
Release profile results

According the results obtained from the in vitro dissolution studies in pH=7.2, it was noted that all formulations provided fast hydration and swelling which resulted in fast formation of an outer swelled gel layer and uniform extended release of the active compound over a period of 12 hours, by both diffusion and erosion pathways. Tablets containing HPMC showed lower levels of released active compound compared with tablets containing PEO as a matrix forming polymer, through the whole interval of 12 hours. PEO matrices provided higher burst release in the interval of 2 hours, and all of them at the end of 12 hours released more than 80% of ascorbic acid. After 2 hour HPMC matrices released 15,21%-16.63% and PEO matrices released 23,17%-28,31%, after 4 hours HPMC matrices released 25,37%-28.41% while PEO matrices released 40,12%-49,90%, after 6 hours HPMC matrices released 35,50%-36.67% and PEO matrices released 52,30%-60,63%, after 8 hours HPMC matrices released 41,51%-47.62%, while PEO matrices released 59,23%-71,14%, after 10 hours HPMC matrices released 53,17%-56.87% and PEO matrices released 70,12%-80,95%, after 12 hours HPMC matrices released 62,85%-68.21%, while PEO matrices released 81,57%-92,47%. All these results could be due to the lover viscosity of PEO1105 compared to HPMC K4M, the lower viscosity of PEO 301 compared to HPMC K15M, and the lower viscosity of PEO mixture compared with HPMC mixture, which lower viscosity of the polymer/s is connected with higher degree of drug diffusion through PEO matrices [Rowe et al, 2006]. Also the higher percentage of released compound in the case of PEO matrices could be connected with the higher portion of eroded polymer which was visually noted in the dissolution vessels where tablets containing PEO were placed. When comparing tablets consisting of HPMC as matrix forming polymer, it was seen that there were no significant differences in the release profiles of batch P1(containing HPMC K4M) and batch P2(containing HPMC K15M) up to 6 hours time period. In the intervals from 6 hours till 12 hours, tablets containing HPMC K4M released slightly higher percent of ascorbic acid compared with matrices made of HPMC K15M. This could be related with the lower molecular weight and viscosity of HPMC K4M compared with HPMC K15M which leads to higher degree of water penetration into the matrix and higher degree of polymer erosion in matrices made of HPMC K4M [ref]. Tablets containing HPMC K4M and

HPMC K15M mixture (P3) in a ratio 1:1 showed similar release profile as the matrices containing single HPMC in the 6 hour interval, while up to 12 hours the % of release vitamin C was somewhere between the % of drug released from tablets containing single HPMC K4M or HPMC K15M. PEO proved to be suitable polymer for developing extended release matrix tablets [Prajapati et al, 2011]. From the gained results it was shown that matrices containing PEO 1105 (P4) showed significantly higher release of active compound through the total period of dissolution testing compared with tablets containing PEO 301(P5). As mentioned before this is due to the lower molecular weight and viscosity of PEO 1105 compared with PE0 301, which leads to higher degree of active substance release by both diffusion and erosion mechanisms . Combining PEO 1105 and PEO 301 (ratio 1:1) in matrix tablets gave very obvious preview of obtaining intermediate viscosity grade polymer mixture and intermediate modified release profile of the active compound. Through all 12 hours P6 batch gave drug release results somewhere between the dissolution results obtained for lower viscosity grade PEO 1105 matrices and higher viscosity PEO 301 matrices. From all the data obtained it could be concluded that tablets containing PEO 1105 as hydrophilic matrix forming polymer were the most suitable option for developing 12 hours extended release matrices of vitamin C treated as food supplement, while matrices containing HPMC are not suitable for this purpose, because of the lower amount (max 68%) of drug released. All results related to the dissolution studies and release profiles of the six batches hydrophilic matrix tablets are shown in table 5 and picture 1.

Table 5- Dissolution profile of all six batches matrix tablets

	P1	**P2**	**P3**	**P4**	**P5**	**P6**
After 2 hours (%)	16,63	15,21	16,57	28,31	23,17	26,91
After 4 hours (%)	25,37	27,11	28,41	49,9	40,12	42,72
After 6 hours (%)	36,57	35,5	34,85	60,63	52,3	53,59
After 8 hours (%)	47,62	41,51	45,36	71,14	59,23	59,64
After 10 hours (%)	56,87	53,17	55,12	80,95	70,12	71,56
After 12 hours (%)	68,21	62,85	67,71	92,47	81,57	82,85



Picture 1- Cumulative drug release of all six batches matrix tablets

Conclusion

Ascorbic acid (Vitamin C) is essential compound for the human health and well-being. The conventional supply of oral vitamin C by standard 500 mg tablets, do not provide satisfactory pharmacological activity because of the high(almost complete) liberated amount of active compound in maximum 30 minutes (PhEur 7), which leads to lower absorption level of this moiety. Also 500 mg supplies of vitamin C are not considered as health supplements but as medicines. The purpose of this study was to develop extended release tablets which will provide slower release of ascorbic acid in smaller doses which could be easily absorbed by the GUT. We imagined and developed our product as direct compressible matrix tablet made from 30% hydrophilic polymer/s, which in contact with water or intestinal fluid will hydrate and swell, and will provide formation of outer gelatinous layer. This gelatinous layer acts as a barrier and modulates the release of the active compound from the matrices by two mechanisms: diffusion and erosion. Six batches of matrix tablets (P1-P6) were prepared and analysed for powder properties, tablet properties and dissolution profile. Hydroxypropyl methylcellulose (HPMC) with different molecular weight and viscosity(HPMC K4M, HPMC K15M and HPMC K4M + HPMC K15M mixture in 1:1 ratio) was used for production of first three batches, while for the 4th ,5th and 6th batch a hydrophilic polymer-resin polyethylene oxide(PEO) was used. Two PEO's- PEO 1105 and PEO 301 with different molecular weight and viscosity, and their mixture in 1:1 ratio were used for preparing the last three batches. On the basis of powder properties, all six batches showed good flowing properties and didn't tend to make any problems during the tableting process. According the results obtained for Carr's index, Hausner ratio and angle of repose batches containing PEO showed better flowability compared with batches containing HPMC. Concerning the results obtained for tablet properties (average mass, hardness, friability, average content), all six batches complied the pharmacopoeial demands. By observing the results gained from the dissolution studies for 12 hours in phosphate buffer pH=7.2, all six batches of matrix tablets hydrated and swelled fast enough, which provided rapid gel-layer formation and uniform continuous delivery of ascorbic acid through 12 hour period. Matrices made of HPMC didn't comply the requirement of min 80% drug liberation through total test period, while all three batches made of PEO released more than 80% of ascorbic acid. This could be due to the lower viscosity of PEO 1105 compared with HPMC K4M, PEO 301 compared with HPMC K15, and PEO mixture compared with HPMC mixture. The lower viscosity of PEO's leaded in formation of weaker gel layer on the surface of the matrix tablets, which provide higher degree of drug release by both diffusion and erosion. By comparing all three batches of PEO matrices it was obviously noted that tablets containing low viscosity PEO 1105 released biggest amount of drug, tablets containing high viscosity PEO 301 released lowest amount of drug, while matrices containing 1:1 mixture of this two resins provided intermediate viscosity and drug release. According the obtained results and our requirements, batch P4 which contains PEO 1105 as matrix forming polymer was our choice for further development of commercially applicable product, because it gave uniform extended release of more than 90% of ascorbic acid in period of 12 hours, demonstrated good powder flowability and complied the pharmacopeial requirement for tablet properties.

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European Pharmacopoeia No.7

United States Pharmacopeia No.35

RAZVOJ I EVALUACIJA FORMULACIJA MATRIKS TABLETA ASKORBINSKE KISELINE SA PRODUŽENIM OSLOBADJANJEM IZRADJENIM SA HIDROFILNIM POLIMERIMA HIDROXIPROPILMETIL CELULOZOM I POLIETILENOKSIDOM

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originalni naučni rad

Sažetak

Cilj: Cilj ovog rada je bio da se razvije formulacija tableta sa kontroliranim oslobadjanjem koje sadrže 350mg Askorbinske kiseline u hidrofilnom matriksu: Hidroksipropilmetil celuloze (HPMC) različitih viskoznosti i u u hidrofilnom matriksu Polietilen oksida razlicitih viskoznosti *Materijale i metode:* Bile su proizvedene šest serija matriks tablet. Korištena je 97% Askorbinska kiselina za direktnu kompresiju kao aktivna supstanca. Kao hidrofilni polimeri koristili su se HPMC K4M, HPMC K15M (Colorcon) I PEO 1105 i PEO 301 (Colorcon).Direktna kompresija je bila izabrana kao postupak izrade. U formulacijama koristila se Mikrokristalna celuloza kao punilo, kopovidon kao sredstvo za vezivanje, koloidalni silicijum dioksid za poboljšanje protočnosti i magnezijum stearat kao lubrikans.
Prije tabletiranja mješavine aktivne i pomočnih supstanci bile su prosijane i odredjena im je nasipna gustina, nasipni ugao, indeks kompresije i Hausner indeks. Dobijenim tabletama odredjivana je prosječna masa, otpornost na lom, habanje, sadržaj aktivne supstance i profil rastvorljivosti u intervalu od 12 sati u fosfatnom puferu. Svi testovi su sprovedeni suglasno

propisima i procedurama opisanim u PhEur7 i USP35.
Rezultati: Svih šest formulacija su imale dobru protočnost, process tabletiranja je protekao bez odstupanja. Dobijene tablet od svih šest fornmulacija odgovarale su farmakopejskim zahtjevima u odnosu na prosječnu masu i variranje mase, otpornost na lom, habanje i sadržaj aktivne komponente. Ispitivanje profila olobadjanja aktivne supstance ukazalo je da svih šest formulacija pokazuju produženo oslobadjanje Askorbinske kiseline u interval od 12 sati; kod formulacija izradjenih sa polietilen oksidima oslobadjanje je bilo veće od 80%. Iz dobijenih rezultata može se konstatirati da polimeri sa nižom viskoznošću daju matrikse iz kojih se aktivna supstanca brže oslobadja u usporedbi sa viskoznijim polimerima, a mješavine polimera PEO 1105/PEO 301 1:1 I HPMC K4M/HPMC K15M 1:1 daju matrikse sa intermedijernim oslobadjanjem što je u skladu sa intermedijernom viskoznosti mješavine polimera.
Zaključak: Od dobijenih rezultata može se zaključiti da tablet koje sadrže PEO 1105 su najpogodniji izbor za izradu tableta Askorbinske kiseline 350mg sa produženim oslobadjanjem u interval od 12 sati.

Ključne riječi: Askorbinska kiselina, tablete sa produženim oslobađanjem, polimer, hidroksipropil metilceluloza, polietilen oksid